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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Gore *et al.*	Confirmation No.:	8928
Serial No.:	10/666,819	Art Unit:	1626
Filed:	September 17, 2003	Examiner:	To be assigned
For:	PROCESS FOR THE PREPARATION OF AROMATIC AZO-COMPOUNDS	Attorney Docket No:	9741-010

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Sir:

Applicants submit herewith certified copy of Great Britain Patent Application No. GB 0221515.0 filed on September 17, 2002, to which the benefit of priority under 35 U.S.C. § 119 is claimed for the above-identified patent application.

No fee is believed to be due for this submission. Should any fee be required, however, please charge any such fee to Deposit Account No. 16-1150.

Respectfully submitted,

Date: February 9, 2004

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Enclosures

By: 
Reg. No. 54,115

The Patent Office
Concept House
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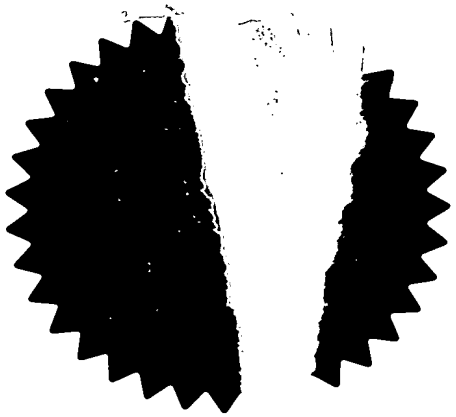

Signed R. Mahoney

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17SEP02 E748787-1 D10032
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1. Your reference ~~GLS~~ OLS/PDJ/1

2. Patent application number
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0221515.0
17 SEP 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*
GENERICS [UK] Ltd.,
Albany Gate, Darkes Lane,
Potters Bar, HERTS,
ENG IAG

Patents ADP number *(if you know it)*
8118747001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention
A Novel Process for the preparation of 3,3'-azo-bis(6-hydroxy-benzoic acid) and its derivatives

5. Name of your agent *(if you have one)*
PRIVATE APPLICANT,

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
DR PAUL JENKINS,
Address as above.

Patents ADP number *(if you know it)*
8465866001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
N/A		

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	—
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11. I/We request the grant of a patent on the basis of this application.

Signature P. D. Jenkins Date 13/9/02

12. Name and daytime telephone number of person to contact in the United Kingdom DR PAUL JENKINS 01707 853249

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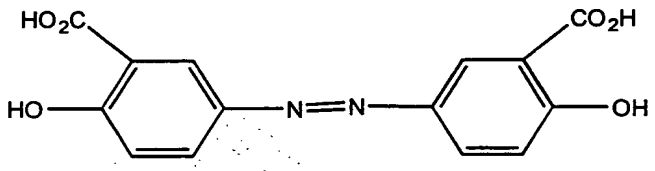
DUPLICATE

A Novel Process for the preparation of 3,3'-azo-bis(6-hydroxybenzoic acid) and its derivatives

The present invention relates to a novel process for the preparation of 3,3'-azo-bis(6-hydroxybenzoic acid) **1** and salts thereof. The process of the current invention is very efficient and enables the preparation of compound **1** and its salts in high yield with low operating costs on a manufacturing scale.



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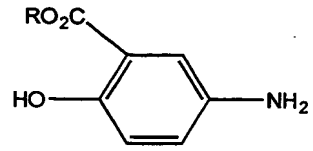
Certain 3,3'-azo-bis(6-hydroxybenzoic acid) derivatives have useful properties and can be used as pharmaceuticals or dyestuffs. One such compound, the disodium salt of 3,3'-azo-bis(6-hydroxybenzoic acid) **I** (olsalazine) is marketed as a pharmaceutical for the treatment of ulcerative colitis.

Processes for the preparation of compound **1**, its salts and derivatives are known and have been disclosed in patents EP 0036636 and DD 276863.

However, the current inventors have developed a process, particularly useful for industrial scale manufacture as it is short, simple and high yielding. The process does not use any hazardous or difficult to handle reagents and is an improvement on currently known processes for the industrial scale manufacture of compound 1, its salts and derivatives.

The current invention is a process for the preparation of 3,3'-azo-bis(6-hydroxybenzoic acid) derivatives and salts thereof comprising the step specified in **Scheme One**, wherein R is a typical ester group such as an alkyl, aryl, or alkyaryl group(*eg* benzyl).



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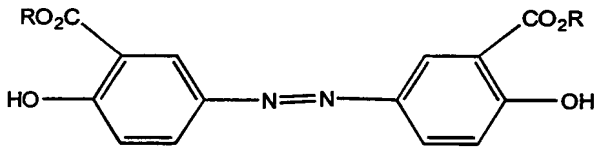
(i) hydrogen peroxide, acetic acid
(ii) conc H_2SO_4



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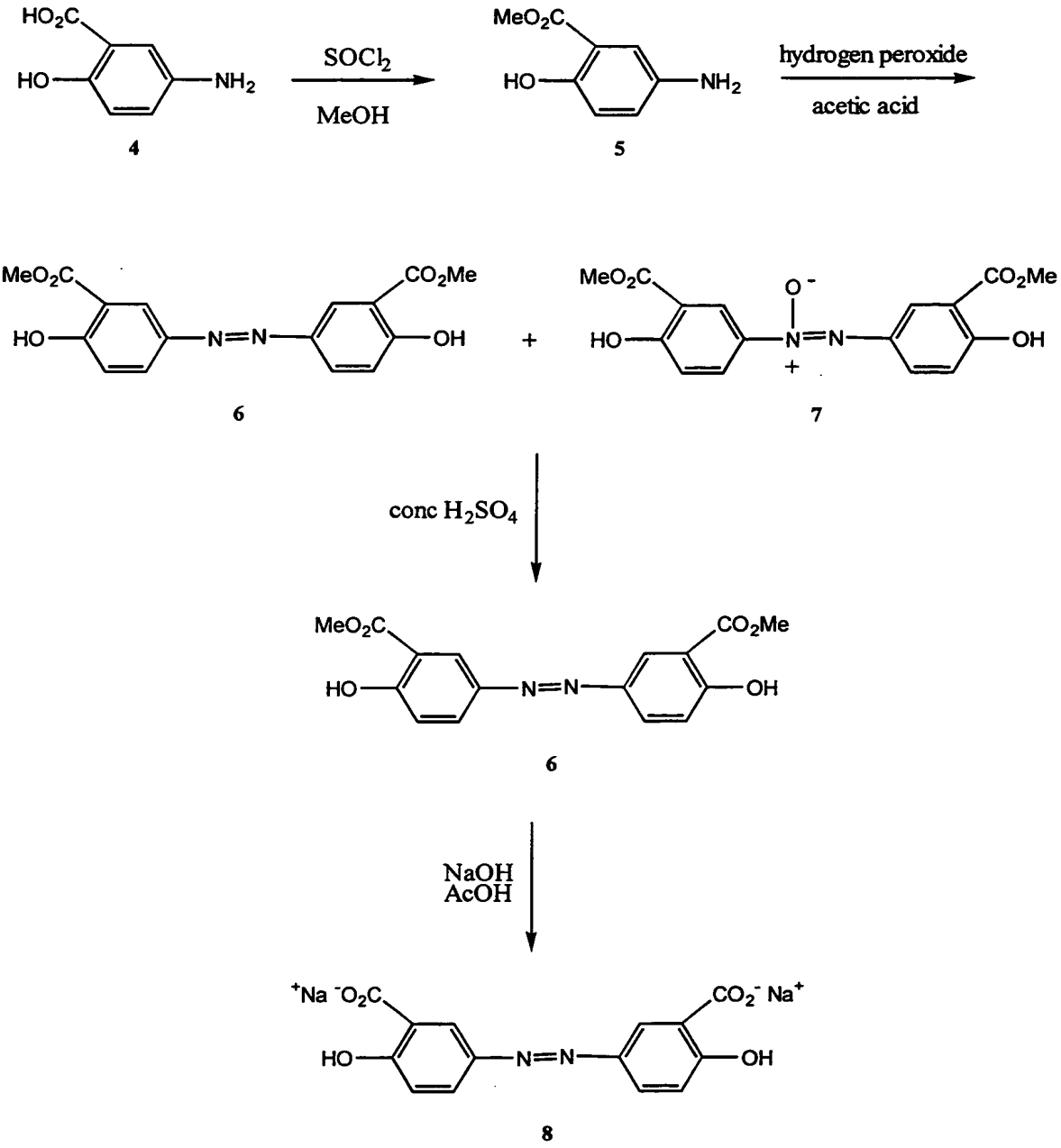
Scheme One

A preferred embodiment of the first aspect of the invention is when R is a lower alkyl group and a particularly preferred embodiment is when R is a methyl group.

An example of the current invention is the preparation of compound **8**, the disodium salt of 3,3'-azo-bis(6-hydroxybenzoic acid) **I** (olsalazine), outlined in **Scheme Two**.

A second aspect of the current invention is the preparation of an azo compound using an oxidation dimerization reaction of an aromatic amino compound or compounds to form the azo linkage. Two different aromatic amines can be used if an asymmetrical azo compound is required. The reagents for the oxidation dimerization reaction are preferably (i) acetic acid/hydrogen peroxide followed by (ii) conc sulphuric acid.



Scheme Two

Further aspects of the current invention are olsalazine **I** and disodium olsalazine **8** when prepared by a process according to the current invention.

The process involves a key oxidation dimerization step to form the azo linkage and to afford the azo compound **6**. This is a novel approach for forming the azo linkage of olsalazine when compared to the prior art. As can be seen from **Scheme Two**, the oxidative dimerization reaction also produces a side product **7** but compound **7** can conveniently be converted to the required product **6** in excellent yield, in the same 'pot', by use of concentrated sulphuric acid.

The process outlined in **Scheme Two** is an example of a procedure comprising the process of the current invention and detailed procedures for this process is found in the experimental section. Compounds of the current invention are also exemplified in **Scheme Two** and in the experimental section.

EXPERIMENTAL PROCEDURE

Methyl 5-amino salicylate (5)

In a 5 litre four neck flask, fitted with reflux condenser, dropping funnel, thermometer pocket and overhead stirrer was charged methanol (3500 ml) and 5-amino salicylic acid **4** (500g, 3.26 moles) with stirring. To the resulting slurry, thionyl chloride (600 ml, 8.16 moles) was added dropwise over a period of two hours by maintaining the temperature of the reaction mass around 35-40°C. After the addition of thionyl chloride was over, the reaction mixture was refluxed for ~15- 16 hrs. Over the period the reaction mixture became brown colored thin slurry. The progress of the reaction was monitored by Thin Layer Chromatography [Stationary phase: silica gel 60 F254, Mobile phase: 5:5:0.5 Acetone: Ethyl acetate: Formic acid v/v, Detection: UV 254nm and iodine vapors]. After 5-amino salicylic acid content decreased below 1.0% (based on TLC), the reaction was worked up as follows. Methanol (2000 ml) was removed by distillation at atmospheric pressure and remaining methanol was swapped with DM water (3 X 1000 ml) under reduced pressure (~200-250 mm of Hg) to get the slurry. This slurry was poured into DM water (3500 ml) and

pH of the solution was adjusted to ~ 5.0 with 25 % (w/v) NaOH solution (~750 ml) and then to 7.0 to 7.5 with 20 % (w/v) Na_2CO_3 solution (~300ml). The recipitated 5-amino methyl salicylate **5** was filtered, washed with water (2 X1000 ml) .The cake was dried at 65°C under reduced pressure (~250 mm of Hg) to constant weight. The yield obtained was 90 % (490g).

M.P.: 93-95°C [Lit. 93-95°C; EP 0291159 awarded to DAK LAB AS (DAK)]

^{1}H-NMR ($CDCl_3$): 3.92 ppm [3H, s, Ar-$COOCH_3$); 6.85 ppm (2H, m, Ar-H); 7.16 ppm (1H, d, J=2.73 Hz, Ar-H);
Mass Spec: M^+ (167), 135, 107 and 79

Dimethyl 3,3'-azo-bis(6-hydroxybenzoate) (6)

To glacial acetic acid (500 ml) was charged 5-amino methyl salicylate **5** (250g, 1.5 mole) while cooling the flask in water bath (28-30°C). The resulting slurry was stirred at 28-30°C for five minutes. To this, aqueous hydrogen peroxide (50%w/v, 300 ml, 4.5 moles) was added over 6 hours. [the reaction flask was immersed in water and maintained at 28-30°C]. As the addition progressed, the slurry slowly changed into dark brown-black coloured homogenous liquid. After the hydrogen peroxide addition was over the reaction mixture was stirred at 28-30°C. The reaction mixture became turbid after ~2-3 hours and a brownish yellow precipitate were observed after 4-5 hours of stirring. After approximately eight hours of stirring, the reaction mass became thick brownish yellow slurry. The reaction mixture was stirred for ~22-24 hours when 5-amino methyl salicylate content was decreased below 1% as seen on TLC. Steps (i) or (ii) could then be followed.

(i) *To isolate the mixture of **6** & **7**, the following procedure was followed:*
To this reaction slurry, was added water (3750ml) and stirred for 25-30 minutes for complete precipitation of mixture of dimethyl 3,3'-azo-bis(6-hydroxybenzoate) **6** and dimethyl 3,3'-azoxy-bis(6-hydroxybenzoate) **7**. The precipitated mixture was the filtered and washed with water (2 X 500 ml). This was then dried at 65°C under reduced pressure (~250 mm of Hg) to constant

weight (moisture content was NMT 1.0%) to get the intermediates mixture in 73 % yield (183g).

^{1}H-NMR ($CDCl_3$): 4.01 ppm [6 H, s, 2 X Ar-$COOCH_3$ (for azo diester)]; 4.02 ppm [6 H, s, 2 X Ar-$COOCH_3$ (for azoxy diester)]; 7.08ppm [2H, d, J=8.8 Hz, C-3 and C-3' Ar-H (for azo diester)]; 7.11 ppm [2H, d, J=8.8 Hz, C-3 and C-3' Ar-H (for azoxy diaester)]; 8.07 ppm (2H, dd, J=8.97 and 2.46 Hz, C-4 and C-4' Ar-H (for azo diaester)]; 8.28 ppm (1 H, dd, J=8.88 and 2.49 Hz, C-4 Ar-H (for azoxy diaester)]; 8.42 ppm (1 H, dd, J=8.88 and 2.49 Hz, C-4' Ar-H (for azoxy diaester)]; 8.44 ppm (2 H, d, J=2.40 Hz, C-6 and C-6' Ar-H (for azo diaester)]; 8.81ppm (1 H, d, J=2.50 Hz, C-6 Ar-H (for azoxy diaester)]; 9.05 ppm (1 H, d, J=2.50 Hz, C-6' Ar-H (for azoxy diaester)]; 11.10 ppm [2 H, s , C-2 and C-2' Ar-OH, (for azo diester)]; 11.15 ppm [1 H, s , C-2 Ar-OH, (for azoxy diaester)] and 11.16 ppm [1 H, s , C-2' Ar-OH, (for azoxy diester)].

Mass Spec: (M^+346 for azoxydiester), (M^+ 330 for Azodiester), 314, 298, 282, 254, 179, 165, 151, 133, 119, 105,91 and 80

(ii) *To proceed directly to pure product* ***6***
Sulfuric acid (conc, 400 ml) was added slowly to the reaction mixture over 2.5 hours. The resulting red coloured slurry was stirred for 10 minutes and then heated to 85-90°C and held at this temperature for 4 hours. The progress of the reaction (disappearance of **7**) was monitored by ^{1}H-NMR. After 4 hours the signal at 9.05 ppm which is characteristic of **7** disappeared. The reaction mass was cooled to 20-25°C and quenched by carefully adding it into cold water [10-15°C, 1500 ml] maintaining the temperature of the quenched mass below 35°C. The quenched mass was stirred for 30 minutes and then filtered. The filter cake was washed with warm water (45-50°C) (2X 200ml) and then with methanol (2 X 50 ml) and suck dried. This was then dried at 80°C under reduced pressure (~250 mm of Hg) to constant weight (moisture content was NMT 2.0%). The yield was 85 % (83g).
M.P.: 223-228°C

^{1}H-NMR ($CDCl_3$): 4.02 ppm (6H, s, C-1 and C-1' Ar-$COOCH_3$); 7.10 ppm (2H, d, J= 8.94 Hz, C-3 and C-3' Ar-H) ; 8.07 ppm (2H, dd, J= 8.94 and 2.46 Hz,

C-4 and -4' Ar-H); 8.44 ppm (2H, d, J= 2.46 Hz, C-6 and C-6' Ar-H); 11.10 ppm (2H, s, C-2 and C-2' Ar--OH, exchanged with D_2O)

Mass Spec: (M^+ 330), 298, 179, 163, 151, 135, 107, 91 and 79

3,3'-azo-bis(6-hydroxybenzoic acid) disodium salt (8)

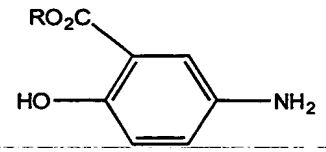
To a solution of sodium hydroxide (48g, 1.2moles in 800 ml of water) was charged compound **6** (80g, 0.24 mole) at 25-30°C. The resulting dark black red colored solution was heated to mild reflux (reaction mixture temperature ~85-90°C) and was held for 90 minutes. This was then treated with activated carbon (Norit Supra A EUR, 3%w/w) and refluxed further for 30 minutes. Then the reaction mixture was cooled to 45-50°C and was filtered through the Celite bed (prepared in water). The celite bed was washed with water (4X 80 ml) and was mixed with the main filtrate. Further 240 ml of water was added to the combined filtrate and washings and cooled to 25-30°C with efficient stirring. The pH of this resulting solution was adjusted to 6.0+/- 0.05 with drop-wise addition of 20% v/v aqueous acetic acid over 30-45 minutes. The resulting yellow slurry was cooled to 0-5°C and stirred for 30 minutes to complete the crystallization; Compound **8** thus obtained was filtered and washed with water (2 X 160 ml) followed by isopropanol wash (40 ml X 2). The wet cake obtained (107g) was dried at 70°C under reduced pressure (~650 mm of Hg) for 16 hours Hg) to constant weight. The title compound **8** was obtained in 65% yield (55 g).

^{1}H-NMR (DMSO-d^6): 6.89 ppm (2H, d, J= 8. 73 Hz, C-3 and C-3' Ar-H); 7.85 ppm; (2H, dd, J= 8. 73 and 2.20 Hz, C-4 and C-4', Ar-H); 8.24 ppm ((2H, d, J= 2.20 Hz, C-6 and C-6' Ar-H)).

Mass Spec: (M^+- 2Na i.e. 302), 284, 266, 214, 165, 137, 121, 109, 93 and 81.

Claims

1. A process for the preparation of 3,3'-azo-bis(6-hydroxybenzoic acid) derivatives and/or salts thereof comprising the following step:



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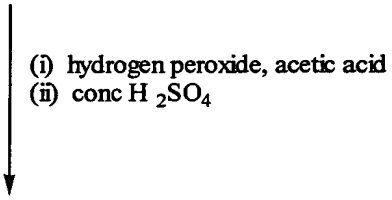

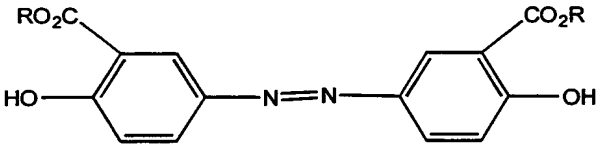

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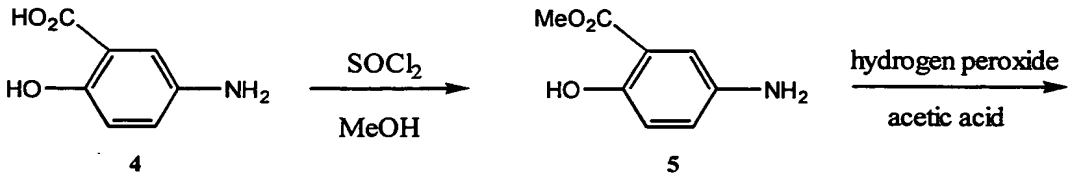
wherein R is a typical ester group such as an alkyl, aryl, or alkyaryl group(*eg* benzyl).

2. The process according to claim 1 wherein R is a lower alkyl group.
3. The process according to claim 2 wherein R is a methyl group.
4. Olsalazine **I** and disodium olsalazine **8** when prepared by a process according to claim 1.
5. A process for the preparation of an azo compound comprising an oxidation dimerization reaction of an aromatic amino compound or compounds to form the azo linkage.
6. The process according to claim 5 wherein two different aromatic amines are used to form an asymmetrical azo compound.
7. The process according to claim 5 or 6 wherein the reagents for the oxidation dimerization reaction are (i) acetic acid/hydrogen peroxide followed by (ii) conc sulphuric acid.

8. A process for the preparation of compound **8**, the disodium salt of 3,3'-azo-bis(6-hydroxybenzoic acid) **I** (olsalazine) comprising the following steps:



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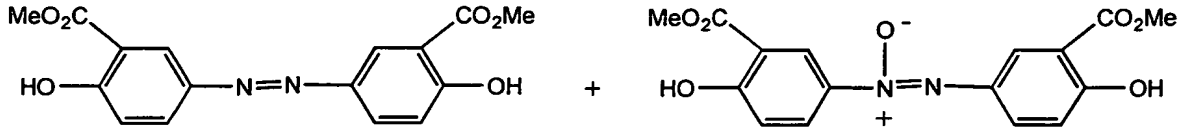

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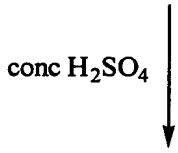

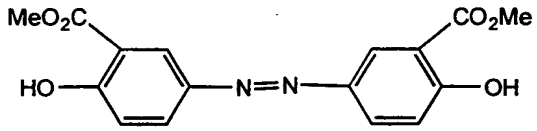

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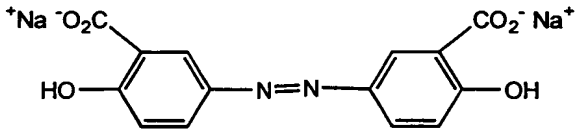

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Abstract

A process for the preparation of 3,3'-azo-bis(6-hydroxybenzoic acid) derivatives and/or salts.